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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In Re:	Patent Application of David Berd	: Confirmation No.: 2699
Appln. No.:	08/203,004	: Group Art Unit: 1643
Filed:	February 28, 1994	: Examiner: Christopher Yaen
For:	COMPOSITION AND METHOD OF USING TUMOR CELLS	: Attorney Docket No.: 061266-5001-03

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Commissioner for Patents
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APPELLANT'S BRIEF UNDER 37 C.F.R. § 41.37

Sir:

This Brief is in furtherance of the Notice of Appeal filed in the above-identified patent application on July 11, 2008. This Brief is accompanied by a Petition for a Five Month Extension of Time, which extends the period for filing this Brief to and through February 11, 2009.

The Director is hereby authorized to charge any required fees, including the appeal brief fee under 37 C.F.R. § 41.20(b)(2), the terminal disclaimer fee under 37 C.F.R. § 1.20(d) and the extension fees under 37 C.F.R. § 1.17(a), or credit any overpayments in connection with this submission to Deposit Account No. **50-0310** (Billing No. 061266-5001-03).

I. REAL PARTY IN INTEREST

The real parties in interest are Thomas Jefferson University ("TJU") and Avax Technologies, Inc. ("Avax"), both of Philadelphia, Pennsylvania. TJU is the assignee of this application. Avax has an exclusive license to this application from TJU.

II. RELATED APPEALS AND INTERFERENCES

Appellant is not aware of any other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Claims 47, 67, 68, 70, 72, 74, 75, and 77 are pending and the final rejection of all of these claims is the subject of this Brief. Claims 1-46, 48-66, 69, 71, 73, and 76 have been cancelled in previously filed amendments during the prosecution of this application. A copy of the text of the claims involved in the appeal is attached as an appendix immediately following this Brief.

IV. STATUS OF AMENDMENTS

Appellant filed an amendment July 11, 2008 in response to the final Office Action dated January 9, 2008. This amendment was denied entry by the Examiner pursuant to the Advisory Action dated October 17, 2008.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 47, from which all other pending claims depend, recites: a method of treating a malignant tumor in a human patient comprising co-administering to the patient (a) a composition comprising a therapeutically effective amount of human tumor cells that: (i) are conjugated to a hapten; (ii) are of the same tumor type as the malignant tumor of said patient for

treatment of whom the composition is intended; (iii) are autologous to said patient; and (iv) have been rendered incapable of growing in the body of a human upon injection therein; and (b) an adjuvant; wherein said malignant tumor is from a cancer selected from the group consisting of melanoma cancer, lung cancer, colon cancer, breast cancer, kidney cancer, and prostate cancer; repeating said administration of said composition for a total of at least six administrations of said composition; and administering a therapeutically effective amount of cyclophosphamide to the patient only prior to the first administration of said composition.

In this regard, embodiments and examples in the specification are disclosed from page 11 to 43. The exemplary embodiments and non-limiting examples disclose a method for treating a malignant tumor in a human patient by co-administration of an adjuvant and a composition comprising human tumor cells (Specification, page 14, lines 4-20; page 15, lines 12-19); wherein the tumor cells are conjugated to a hapten (Specification, page 14, lines 17-18), are of the same tumor type as the malignant tumor of the patient (Specification, page 11, line 27-page 12, line 1), are autologous to the patient (Specification, page 12, line 5), and have been rendered incapable of growing the body of a human upon injection therein (Specification, page 19-22); wherein the malignant tumor is selected from the group consisting of melanoma cancer, lung cancer, colon cancer, breast cancer, kidney cancer, and prostate cancer (Specification, page 11, lines 23); wherein the administration is repeated for a total of at least six administrations (Specification, page 14, lines 25-26; page 22, lines 25-26); and wherein a dose of cyclophosphamide is given to the patient prior to the first administration (Specification, page 18, lines 3-6 and 16-17).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

a. Whether claims 47, 67, 68, 70, 72, 74, 75, and 77 are unpatentable under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not contain a written description of the claimed invention;

b. Whether claims 47, 67, 68, 70, 72, 74, 75, and 77 are unpatentable under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,484,596 to Hanna, Jr. et al.

("Hanna") in view of Abstract 1515, *Proc AACR* 1989:30:382 ("Berd 1989"), U.S. Patent No. 5,651,993 to Edelson et al. ("Edelson"), *Immunology*, 3rd ed., 1993, p. 2.10 ("Riott"), U.S. Patent No. 5,008,183 to Osther ("Osther"), and *J. Immunol.* 1970:19:189-203 ("Geczy"); and

c. Whether claims 47, 67, 68, 70, and 74 are unpatentable under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-10 of U.S. Patent No. 6,458,369 to Berd ("Berd").

VII. ARGUMENT

Whether the rejections under 35 U.S.C. § 112, first paragraph, are improper:

Claims 47, 67, 68, 70, 72, 74, 75, and 77 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not contain a written description of the claimed invention (Final Office Action, dated January 9, 2008, sections 5 and 9).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. MPEP § 2163.02.

The Examiner asserts that the limitation of "repeating said administration of said composition for a total of at least six administrations of said composition," as recited in claim 47, has no clear support in the specification or claims as originally filed. Appellant respectfully disagrees.

Page 18, lines 3-19 of the specification describes an embodiment of the invention wherein patients are treated using an immunotherapy regimen including a vaccine of hapten-conjugated autologous tumor cells and a low dose cyclophosphamide pretreatment. Lines 13-16

specify that the patients who are considered to be deriving benefit from the therapy are continued on the immunotherapy regimen without indicating a limit to the number of subsequent vaccine doses that may be administered. One non-limiting example in the specification describes an embodiment where patients were given a minimum of six treatments (page 22, lines 25-26). Additional non-limiting embodiments are provided showing that patients may receive more than six treatments (page 14, lines 25-26; page 19, lines 12-13; page 23, lines 25-26; page 25, lines 25-27; page 29, line 20; page 32, lines 10-11; page 41, lines 22-23). From these described embodiments, one of ordinary skill in the art would have recognized that Appellant was in possession of the claimed method, in particular, wherein said administration is repeated for a total of at least six administrations. See also *Ralston Purina Company v. Far-Mar-Co, Inc.*, 222 USPQ 863 (D. Kan. 1984) and *Ralston Purina Company v. Far-Mar-Co., Inc.*, 227 USPQ 177 (Fed. Cir. 1985), which held that a limitation of "at least about 212°F" was sufficiently supported by a disclosure teaching the heating of a mixture and an example setting forth the specific range of 212-380°F.

The Examiner further asserts that the limitation of "administering a therapeutically effective amount of cyclophosphamide to the patient only prior to the first administration of said composition," as recited in claim 47, has no clear support in the specification or claims as originally filed. Appellant respectfully disagrees and submits that explicit support for this limitation may be found at least on page 18 of the specification as filed.

For example, as described on page 18, lines 3-6 of the specification, one embodiment of the invention includes treating patients with an immunotherapy regimen including a vaccine of hapten-conjugated autologous tumor cells and a low dose cyclophosphamide pretreatment. As further described on lines 13-17, patients who are considered to be deriving benefit from the therapy are continued on the immunotherapy regimen, wherein "[s]ubsquent vaccines may be given without cyclophosphamide" (emphasis added). One of ordinary skill in the art would have therefore recognized that Appellant was in possession of the claimed method, in particular, wherein cyclophosphamide is administered to the patient only prior to the first administration of the tumor cell composition.

In view of the foregoing, Appellant respectfully submits that the specification conveys with reasonable clarity to those skilled in the art that Applicant was in possession of the invention as claimed, and Appellant respectfully requests the rejections be withdrawn.

Whether the rejections under 35 U.S.C. § 103(a) are improper:

Claims 47, 67, 68, 70, 72, 74, 75, and 77 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,484,596 to Hanna, Jr. et al. ("Hanna") in view of Abstract 1515, *Proc AACR* 1989:30:382 ("Berd 1989"), U.S. Patent No. 5,651,993 to Edelson et al. ("Edelson"), *Immunology*, 3rd ed., 1993, p. 2.10 ("Riott"), U.S. Patent No. 5,008,183 to Osther ("Osther"), and *J. Immunol.* 1970:19:189-203 ("Geczy"). (Final Office Action, dated January 9, 2008, section 7; non-final Office Action, dated May 11, 2007, section 17).

As set forth in section 17 of the non-final Office Action mailed May 11, 2007, the Examiner asserts that Hanna teaches a method of treating a malignant tumor in a human patient comprising administering autologous irradiated tumor cells in combination with an adjuvant. The Examiner specifically notes, however, that Hanna does not teach a composition comprising haptenized tumor cells, does not teach administering a therapeutically effective amount of cyclophosphamide prior to administration of the composition, and does not teach administration of the composition at least six times. (Non-final Office Action, dated May 11, 2007, page 28).

Berd 1989 allegedly teaches a vaccine comprising autologous, irradiated melanoma cells haptenized with DNP and mixed with BCG. The Examiner argues that it would have been obvious to one of ordinary skill in the art to have substituted the colon cancer cells of Hanna in the method of Berd 1989 in order to produce a composition comprising DNP-haptenized colon cancer cells. (Non-final Office Action, dated May 11, 2007, page 30). The Examiner also asserts that Berd 1989 teaches that cyclophosphamide is administered prior to the first administration of the DNP-haptenized autologous irradiated melanoma cells. (Final Office Action, dated January 9, 2008, page 5).

Appellant respectfully points out that Berd 1989 does not provide any description demonstrating how the DNP-haptenized autologous irradiated melanoma cells were actually

prepared, and therefore even if combined with Hanna, Appellant respectfully submits that the reference is insufficient to lead one of ordinary skill in the art to the claimed invention.

For example, there is no disclosure in Berd 1989 of how the melanoma cells were obtained, no disclosure of how the melanoma cells were conjugated to DNP, and there is no disclosure of the amount of BCG used in the vaccine. As particularly discussed in Section 9 of the Declaration under 37 C.F.R. § 1.132 of Donald P. Braun, Ph.D., filed May 29, 2001, Berd 1989 does not provide a definitive protocol, does not describe the route of administration, does not provide an adequate a schedule of vaccination, and does not state how conjugation to DNP was performed. Without such details, one of ordinary skill in the art would have been unable to practice the technology predictably with a reasonable expectation of success, and given the lack of disclosure supplied by Berd 1989, one of ordinary skill in the art would not have been enabled to produce the DNP-haptenized colon cancer cell composition proposed by the Examiner without further guidance.

With regards to the argument that Berd 1989 is deficient because it does not provide a definitive protocol for administration of the cells or describe an effective protocol and therefore cannot provide a reasonable expectation of success, the Examiner writes on page 35 of the non-final Office Action, dated May 11, 2007, that the skilled artisan would have looked particularly to Cancer Research 46, 2572-2577, May 1986 ("Berd et al.") "for guidance drawn to the definitive and effective protocol."

As an initial matter, the Examiner has not resolved the basic factual inquiries of *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) with respect to the teachings of Berd et al., and it is therefore unclear whether this reference is being applied in combination with the other cited art in making the rejection under 35 U.S.C. § 103(a).

Nevertheless, if one of ordinary skill in the art would have looked particularly to the teachings of Berd et al. for the "definitive and effective protocol," as specifically asserted by the Examiner, the skilled artisan would have been led away from the claimed method because Berd et al. explicitly teaches the administration of cyclophosphamide prior to *each* vaccine administration (Berd et al., Table 3, page 2573), whereas the claimed invention administers the

cyclophosphamide *only* prior to the first administration. Furthermore, Appellant respectfully points out that Berd et al. does not make up for all the deficiencies of Berd 1989 because it does not teach how to make *hapten-conjugated* autologous melanoma cells. None of the other references relied upon by the Examiner, either alone or in combination, make up for these deficiencies.

Edelson is relied upon by the Examiner for teaching that conventional vaccination relies upon inoculation of a patient with an antigen to establish a primary immune response and that frequent exposure to antigen quickly boosts the level of memory cells. Riott is relied upon by the Examiner for teaching that T-memory cells are produced. Geczy is relied upon by the Examiner solely "to provide a nexus between and demonstration of the functional identity" of DNCB and DNFB. (Non-Final Office Action, dated May 11, 2007, section 17). None of these references are directed to methods of treating a malignant tumor in a patient, and the Examiner has not demonstrated how the teachings of these references can be combined to make up for the above-identified deficiencies of Hanna and Berd 1989. For example, none of these references disclose, teach or suggest administering a composition comprising tumor cells to a patient at least six times, nor do they enable one of ordinary skill in the art to predictability make a composition comprising DNP-haptenized colon cancer cells, as proposed by the Examiner, with any reasonable expectation of success.

Osther is relied upon by the Examiner to teach "conventional immunizing protocols" (Final Office Action, dated January 9, 2008, page 5). In particular, the Examiner asserts that Osther teaches conventional methods of immunization wherein boosting is used to increase titers of antibodies, and the Examiner specifically points to Osther, col. 5, lines 50-54, which describes giving between two and six booster injections to reach optimal antibody titers. The Examiner concludes that, given these "conventional boosting protocols," it would have been obvious to one of ordinary skill to have repeated the administration of a composition of tumor cells to a patient at least six times. (Non-final Office Action, dated May 11, 2007, page 32).

Appellant respectfully notes that Osther relates specifically to the use of a non-human immune antibody in an assay system for detecting the presence or absence of antibodies to viral

and/or bacterial infective agents (col. 1, lines 7-11). More particularly, Osther is directed to a method for producing a desired antibody in a non-human animal (col. 2, line 53-55; col. 3, lines 28-31), the method comprising vaccinating the animal with a preparation of viral lysate and an adjuvant, and giving booster immunizations of viral proteins without adjuvant (col. 3, lines 36-59). The teachings of Osther at col. 5, lines 50-54, which is particularly relied upon by the Examiner, relates specifically to a method for preparing porcine immune IgG against HIV-1, wherein a Yorkshire breed pig was immunized with HIV-1 antigen lysate and given subsequent booster vaccines. It is further noted that the pig received a total of 5 vaccinations before it was sacrificed and its blood harvested (col. 5, lines 20-22).

Appellant respectfully submits that one of ordinary skill in the art would not have looked to the teachings Osther in developing a method for treating a malignant tumor in a human patient. As discussed above, Osther relates to the production of antibodies against viral antigens, which are useful as diagnostic reagents. In particular, Osther is concerned with the production of optimal antibody titers in a non-human animal against viral antigens. Oster does not teach, either implicitly or explicitly, any methods related to or useful for the treatment of cancer or the production and use of haptenized tumor cells. The teachings of Osther are clearly irrelevant to immunotherapy regimes for treating a malignant tumor in a human patient, and accordingly, one of ordinary skill in the art would have no reason to combine the teachings of Osther with the teachings of Hanna, Berd 1989, and the other references to arrive at Appellant's claimed invention. Moreover, even when combined, Osther does not make up for the deficiences of Hanna and Berd 1989.

In view of the foregoing, Appellant respectfully submits that one of ordinary skill in the art would not have combined the cited references as proposed by the Examiner. Furthermore, even when forcibly combined in the manner suggested by the Examiner, the references are insufficient to teach or suggest all the limitations of the claims and they would not have enabled one of ordinary skill in the art to have arrived at the claimed invention with any reasonable expectation of success or predictability. Accordingly, withdrawal of the rejection is respectfully requested.

Double-Patenting:

Claims 47, 67, 68, 70, and 74 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3-10 of U.S. Patent No. 6,458,369 ("Berd"). (Final Office Action, dated January 9, 2008, section 8).

A Terminal Disclaimer directed to Berd was submitted with the Amendment filed July 11, 2008. Because the Amendment was denied entry, Appellant submits herewith a new Terminal Disclaimer directed to Berd. Accordingly, this rejection is now moot.

Conclusion:

In view of the foregoing, Appellant respectfully submits that the rejections made in the final Office Action are in error or rendered moot and therefore should be withdrawn.

Respectfully submitted,

DAVID BERD

Date: February 11, 2009 By: /Richard L. Leung/

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VIII. CLAIMS APPENDIX

1.-46. (Cancelled)

47. A method of treating a malignant tumor in a human patient comprising co-administering to the patient

(a) a composition comprising a therapeutically effective amount of human tumor cells that:

(i) are conjugated to a hapten;

(ii) are of the same tumor type as the malignant tumor of said patient for treatment of whom the composition is intended;

(iii) are autologous to said patient; and

(iv) have been rendered incapable of growing in the body of a human upon injection therein; and

(b) an adjuvant;

wherein said malignant tumor is from a cancer selected from the group consisting of melanoma cancer, lung cancer, colon cancer, breast cancer, kidney cancer, and prostate cancer;

repeating said administration of said composition for a total of at least six administrations of said composition; and

administering a therapeutically effective amount of cyclophosphamide to the patient only prior to the first administration of said composition.

48.-66. (Cancelled)

67. The method of claim 47, wherein said hapten is selected from the group consisting of dinitrophenyl, trinitrophenyl, and N-iodoacetyl-N'-(5-sulfonic 1 -naphtyl) ethylene diamine.

68. The method of claim 47 wherein said hapten is dinitrophenyl.

69. (Cancelled)

70. The method of claim 47, wherein administering a therapeutically effective amount of cyclophosphamide comprises administering a dose of about 300 mg/M^2 of cyclophosphamide prior to the first administration of said composition.

71. (Cancelled)

72. The method of claim 47 further comprising sensitizing the patient with a therapeutically effective amount of 1 -fluoro-2,4-dinitrobenzene prior to administering cyclophosphamide.

73. (Cancelled)

74. The method of claim 47 wherein said adjuvant is Bacillus Calmette-Guerin.

75. The method of claim 47 wherein said administration of said composition prolongs survival of said patient.

76. (Cancelled)

77. The method of claim 47, wherein said administration of said composition elicits T lymphocytes that infiltrate the tumor of said human.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.